

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00023

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 21/05, G01N 21/85, B05D 1/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01B, G01J, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5518759 A (SEVILLANO ET AL), 21 May 1996 (21.05.96), figures 1,7	1,2,24,25
Y	figures 1,7 --	3,4,26
Y	WATANO,S.et al."CONTROL OF GRANULATION PROCESS BY FUZZY LOGIC".IN:NORTH AMERICAN FUZZY INFORMATION, 1999.18TH.INTERNATIONAL CONFERENCE OF THE,NAFIPS On pages:905-908, 10-12 June 1999.fig.2 --	3,26
Y	T.Laurell et al."DESIGN AND DEVELOPMENT OF A SILICON MICROFABRICATED FLOW-THROUGH DISPENSER FOR ON-LINE PICOLITRE SAMPLE HANDLING". J.MICROMECH.MICROENG.9(1999)369-376.Printed in the UK.Abstract. --	4

☒ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

* Special categories of cited documents	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

20 April 2001

Date of mailing of the international search report

30-04-2001

Name and mailing address of the ISA/
 Swedish Patent Office
 Box 5055, S-102 42 STOCKHOLM
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Authorized officer

Sture Elnäs/LR

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00023

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 003229 A1 (ASTRA AKTIEBOLAG), 20 January 2000 (20.01.00), abstract -----	1,2,7-20, 21-25,31-41

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/04/01

International application No.
PCT/SE 01/00023

Patent document cited in search report			Publication date	Patent family member(s)	Publication date	
US	5518759	A	21/05/96	US	5405645 A	11/04/95
WO	003229	A1	20/01/00	NONE		

89/1806995
5000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



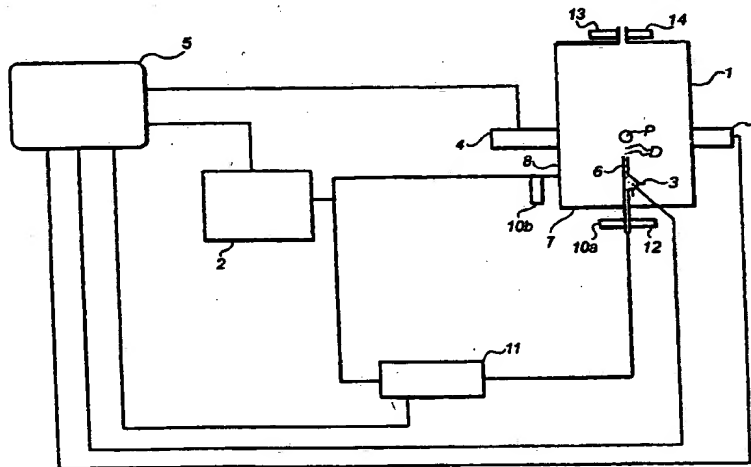
(43) International Publication Date
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number
WO 01/51915 A1

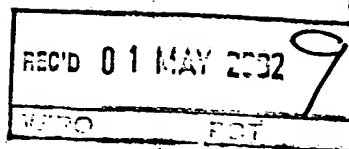
- (51) International Patent Classification⁷: G01N 21/05, 21/85, B05D 1/38
- (21) International Application Number: PCT/SE01/00023
- (22) International Filing Date: 8 January 2001 (08.01.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0000090-1 13 January 2000 (13.01.2000) SE
- (71) Applicant (for all designated States except US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FOLESTAD, Staffan [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). NIKLASSON, Björn, Ingela [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). RASMUSON, Anders [SE/SE]; Gustavsgatan 19, S-431 66 Mölndal (SE). STRÖM, Daniel [SE/SE]; Chalmers Tekniska Högskola, Institutet för Kemisk apparat- och anläggningsteknik, S-412 96 Göteborg (SE).
- (74) Agent: ASTRAZENECA AB; Global Intellectual Property, S-151 85 Södertälje (SE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND APPARATUS FOR MONITORING THE COATING ON A PARTICLE DURING MANUFACTURING OF A PHARMACEUTICAL PRODUCT



(57) Abstract: In a method of monitoring the formation of a coating on a single particle (P), an apparatus is used which comprises means (2, 5, 6, 9) for arranging said particle (P) at a given spatial location, and a fluid supply unit (3) adapted to apply a coating fluid to the particle (P) such that the coating is formed. Further, the apparatus has a measurement unit (4) which is adapted to perform a spectrometric measurement on the coating during formation thereof, and to derive a measurement value of at least one principal parameter related to the coating. Thus, such principal parameters, for example thickness, thickness growth rate and physical and/or chemical properties related to the quality of the coating, as well as heat, mass and momentum transfer, can be continuously and non-invasively monitored during the coating process on the single particle (P). The results of such measurements can be used to understand the coating process on the single particle (P), and ultimately to control, up-scale and develop industrial full-scale coating plants.

WO 01/51915 A1



09/1806795

Applicant's or agent's file reference A2294-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE01/00023	International filing date (day/month/year) 08-01-2001	Priority date (day/month/year) 13-01-2000
International Patent Classification (IPC) or national classification and IPC ₇ G01N 21/05, G01N 21/85, B05D 1/38		
Applicant ASTRAZENECA AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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Date of submission of the demand 19-07-2001	Date of completion of this report 23-04-2002
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Sture Elnäs /itw Telephone No. 08-782 25 00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☐ the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement) under article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☐ contained in the international application in written form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☐ The amendments have resulted in the cancellation of:**☐ the description, pages _____☐ the claims, Nos. _____☐ the drawings, sheet/fig _____**5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1).

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Priority is considered valid, therefore document WO 0003229 is of no relevance.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims	<u>1-41</u>	YES
	Claims		NO
Inventive step (IS)	Claims	<u>1-41</u>	YES
	Claims		NO
Industrial applicability (IA)	Claims	<u>1-41</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The most relevant documents cited in the International Search Report are:

D1: US 5518759

D2: Watano, S. et al. "Control of granulation process by fuzzy logic". In: North American Fuzzy Information, 1999.

D3: Laurell, T. et al. "Design and development of a silicon microfabricated flow-through dispenser for on-line picolitre sample handling". J.Micromech.Microeng. 9(1999).

D1 describes a process and an apparatus for monitoring and controlling the formation of a coating on a substrate. In the method, the substrate is given a spatial location. The process is monitored by continuously performing spectrometric measurements during the formation.

D2 discloses a device for control of a granulation process. The method comprises a fluidized bed used for the granule growth. The process is furthermore on-line monitored and measured by a CCD camera.

D3, also cited in the description, discloses a device for generating droplets.

D1 is closest to describing the invention. The invention as claimed in claims 1, 21, 22, 23 and 24 differs from D1 in respect of defining the object of the formation as "a single particle". D1 discloses a substrate in the shape of a flat surface, which is placed near or within a plasma cloud. Furthermore, in the invention claimed, the object of the spectrometric measurement is the coating, not the coating fluid, while in D1 the spectrometer is used to monitor the bulk or center area of the plasma ball. Consequently, the invention as claimed in claims 1, 21, 22, 23 and 24 fulfills the requirement of novelty. ... / ...

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

The cited prior art does not give any indication that would lead a person skilled in the art to the claimed method of, and apparatus for monitoring the formation of a coating on a single particle. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1- 41 is novel and is considered to involve an inventive step. The invention is industrially applicable.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 003229	20-01-2000	07-07-1999	13-07-1998

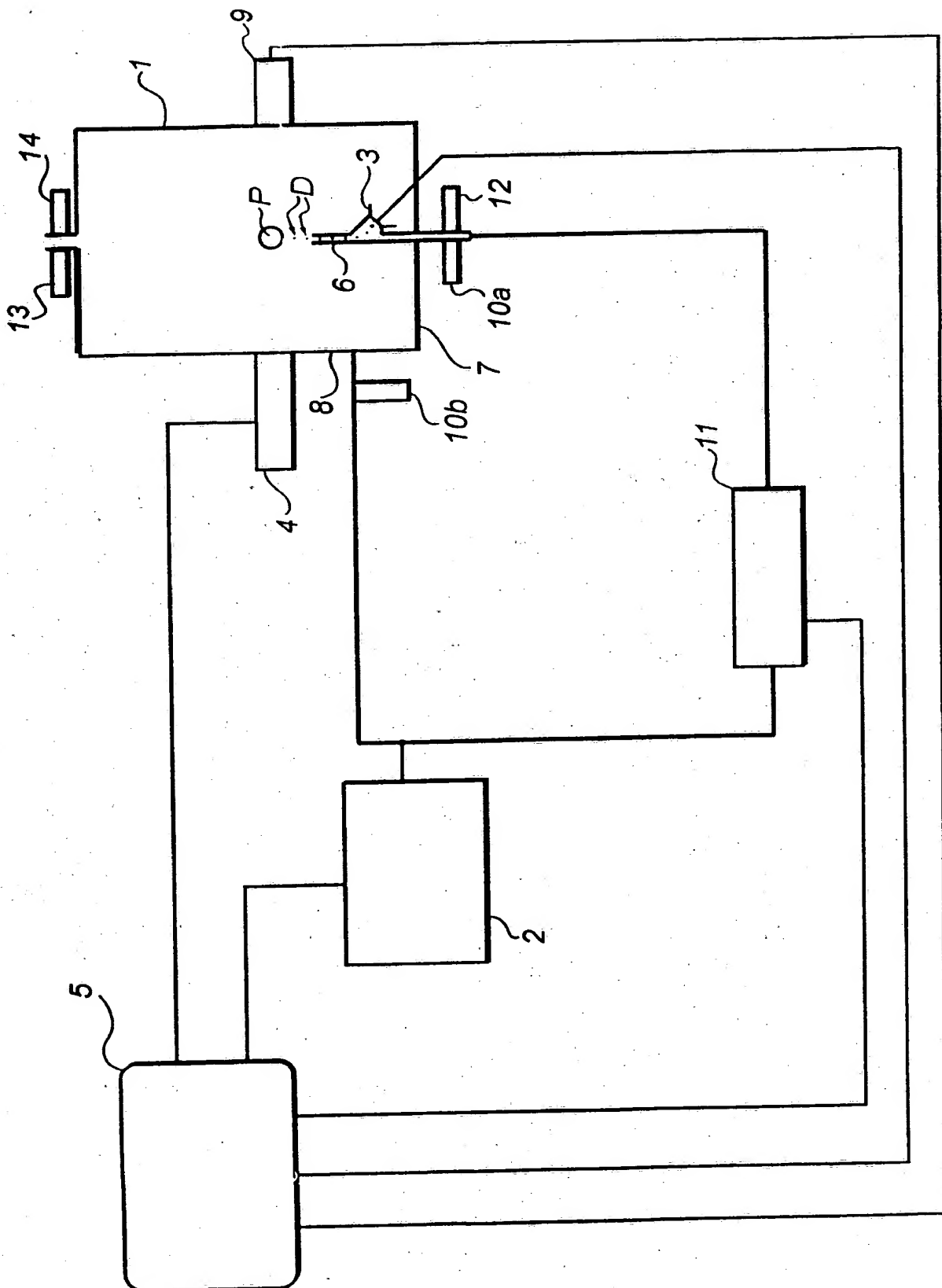
2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure

Date of non-written disclosure
(day/month/year)

Date of written disclosure
referring to non-written disclosure
(day/month/year)

1/1



PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) A2294-1 WO

Box No. I TITLE OF INVENTION

METHOD AND APPARATUS FOR MONITORING

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.

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Facsimile No.

+46 8 553 288 20

Teleprinter No.

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

FOLESTAD, Staffan
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Global Intellectual Property
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S-151 85 Södertälje
Sweden

Telephone No.

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Facsimile No.

+46 8 553 288 20

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>NIKLASSON BJÖRN, Ingela AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>RASMUSON, Anders Gustavsgatan 19 S-431 66 Mölndal Sweden</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>STRÖM, Daniel Chalmers Tekniska Högskola Institutet för Kemisk apparat- och anläggningsteknik S-412 96 Göteborg Sweden</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality:	State (that is, country) of residence:
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><input type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.</p>	

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LC Saint Lucia |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda | <input checked="" type="checkbox"/> LK Sri Lanka |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LR Liberia |
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| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MZ Mozambique |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | Check-box reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> KR Republic of Korea | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)


Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 13 January 2000 (13.01.2000)	0000090-1	Sweden (SE)		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / SE		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office) 16 October 2000 SE00/00023 Sweden	

Box No. VIII CHECK LIST; LANGUAGE OF FILING	
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 10 claims : 6 abstract : 1 drawings : 1 sequence listing part of description : Total number of sheets : 22	This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: GF3739/2000 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): ITS Report SE00/00023
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT	
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). Södertälje, 5 January 2001  Eva Selin Global Intellectual Property, AstraZeneca AB	

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau:

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A2294-1 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE01/00023	International filing date (day/month/year) 08-01-2001	Priority date (day/month/year) 13-01-2000
International Patent Classification (IPC) or national classification and IPC ₇ G01N 21/05, G01N 21/85, B05D 1/38		
Applicant ASTRAZENECA AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 19-07-2001	Date of completion of this report 23-04-2002
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Form PCT/IPEA/409 (cover sheet) (January 1998)	Authorized officer Sture Elnäs /itw Telephone No. 08-782 25 00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1).

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Priority is considered valid, therefore document WO 0003229 is of no relevance.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims	<u>1-41</u>	YES
	Claims		NO
Inventive step (IS)	Claims	<u>1-41</u>	YES
	Claims		NO
Industrial applicability (IA)	Claims	<u>1-41</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The most relevant documents cited in the International Search Report are:

D1: US 5518759

D2: Watano, S. et al. "Control of granulation process by fuzzy logic". In: North American Fuzzy Information, 1999.

D3: Laurell, T. et al. "Design and development of a silicon microfabricated flow-through dispenser for on-line picolitre sample handling". J.Micromech.Microeng. 9(1999).

D1 describes a process and an apparatus for monitoring and controlling the formation of a coating on a substrate. In the method, the substrate is given a spatial location. The process is monitored by continuously performing spectrometric measurements during the formation.

D2 discloses a device for control of a granulation process. The method comprises a fluidized bed used for the granule growth. The process is furthermore on-line monitored and measured by a CCD camera.

D3, also cited in the description, discloses a device for generating droplets.

D1 is closest to describing the invention. The invention as claimed in claims 1, 21, 22, 23 and 24 differs from D1 in respect of defining the object of the formation as "a single particle". D1 discloses a substrate in the shape of a flat surface, which is placed near or within a plasma cloud. Furthermore, in the invention claimed, the object of the spectrometric measurement is the coating, not the coating fluid, while in D1 the spectrometer is used to monitor the bulk or center area of the plasma ball. Consequently, the invention as claimed in claims 1, 21, 22, 23 and 24 fulfills the requirement of novelty. / ...

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 003229	20-01-2000	07-07-1999	13-07-1998

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure

Date of non-written disclosure
(day/month/year)Date of written disclosure
referring to non-written disclosure
(day/month/year)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/00023

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

The cited prior art does not give any indication that would lead a person skilled in the art to the claimed method of, and apparatus for monitoring the formation of a coating on a single particle. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1- 41 is novel and is considered to involve an inventive step. The invention is industrially applicable.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

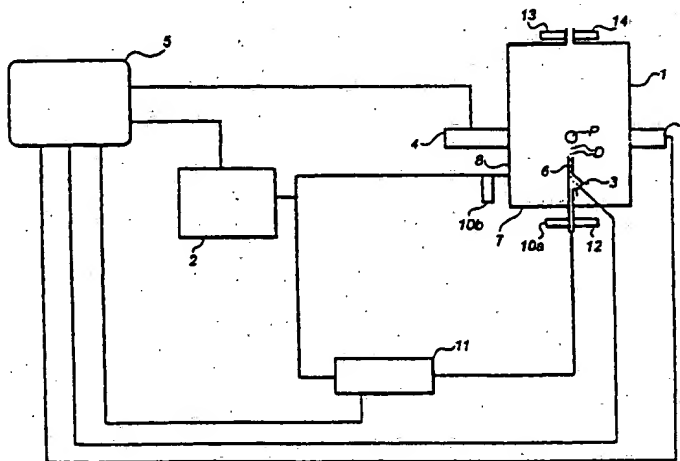


(43) International Publication Date
19 July 2001 (19.07.2001)

PCT

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WO 01/51915 A1

- (51) International Patent Classification⁷: G01N 21/05, 21/85, B05D 1/38
- (21) International Application Number: PCT/SE01/00023
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- (25) Filing Language: English
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- (30) Priority Data:
0000090-1 13 January 2000 (13.01.2000) SE
- (71) Applicant (for all designated States except US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FOLESTAD, Staffan [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). NIKLASSON, Björn, Ingela [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). RASMUSON, Anders [SE/SE]; Gustavsgatan 19, S-431 66 Mölndal (SE). STRÖM, Daniel [SE/SE]; Chalmers Tekniska Högskola, Institutet för Kemisk apparat- och anläggningsteknik, S-412 96 Göteborg (SE).
- (54) Title: METHOD AND APPARATUS FOR MONITORING THE COATING ON A PARTICLE DURING MANUFACTURING OF A PHARMACEUTICAL PRODUCT
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



(57) Abstract: In a method of monitoring the formation of a coating on a single particle (P), an apparatus is used which comprises means (2, 5, 6, 9) for arranging said particle (P) at a given spatial location, and a fluid supply unit (3) adapted to apply a coating fluid to the particle (P) such that the coating is formed. Further, the apparatus has a measurement unit (4) which is adapted to perform a spectrometric measurement on the coating during formation thereof, and to derive a measurement value of at least one principal parameter related to the coating. Thus, such principal parameters, for example thickness, thickness growth rate and physical and/or chemical properties related to the quality of the coating, as well as heat, mass and momentum transfer, can be continuously and non-invasively monitored during the coating process on the single particle (P). The results of such measurements can be used to understand the coating process on the single particle (P), and ultimately to control, up-scale and develop industrial full-scale coating plants.

WO 01/51915 A1

METHOD AND APPARATUS FOR MONITORING THE COATING ON A PARTICLE DURING MANUFACTURING OF A PHARMACEUTICAL PRODUCT

Technical field

The present invention relates to a method and apparatus for monitoring the formation of a coating on a particle. Ultimately, the invention is focused on controlling the process of manufacturing a coating of a pharmaceutical product, such as a pellet, a tablet or a capsule.

Technical background

Generally, a coating of a pharmaceutical product consists of one or more films and each film consists of one or more layers. Below, "coating" is used as a comprehensive expression encompassing everything from an individual layer to a combination of several different films. Each film is the result of a single coating step, generally performed in a coating vessel, where for instance layers of the film are built up. The coating process takes place either in a fluidized bed wherein particles, so-called nuclei, are sprayed with a specific coating liquid, or by passing the particles through a spray dust of said liquid. Several other generally used coating techniques are known in the prior art, such as melting, aggregation etc. The total process of manufacturing a complete coating may involve a plurality of such coating steps. However, the process may as well be sequential, whereby the whole process represents a continuous flow.

Pharmaceutical products are coated for several reasons. A protective coating normally protects the active ingredients from possible negative influences from the environment, such as for example light and moisture but also temperature and vibrations. By applying such a coating, the active substance is protected during storage and transport. A coating could also be applied to make the product easier to swallow, to provide it with a pleasant taste or for identification of the product. Further, coatings are applied which perform a pharmaceutical function such as conferring enteric and/or controlled release. The purpose of a functional coating is to provide a pharmaceutical preparation or formulation with desired properties to enable the transport of the active pharmaceutical substance through the digestive system to the region where it is to be released and/or absorbed. A desired concentration profile over time of the active substance in the body may be obtained by such a controlled course of release. An enteric coating is used to protect the product from disintegration in the acid environment of the stomach. Moreover, it is important that the desired functionalities are constant over time, i.e. during storage. By controlling the

quality of the coating, the desired functionalities of the final product may also be controlled.

5 There are strict requirements from the different Registration Authorities on pharmaceutical products. These requirements will put high demands on the quality of the coating and require that the complex properties of the coating will be kept within narrow limits. In order to meet these demands, there is a need for accurate control of the coating process.

10 The quality of the coating depends on physical and/or chemical properties of the coating, such as chemical composition, local inhomogeneities, physical and chemical homogeneity, density, mechanical properties, static parameters, modulus, tensile strength, elongation at break, compression, ductility, viscoelastic parameters, morphology, macro- and microscopic properties, amorphous and/or crystallinity, permeability, porosity, 15 aggregation, wettability, degree of coalescence/maturity, stability and ability to resist chemical and/or physical degradation. There are also other properties not listed above. The quality of the coating affects to a great extent the release properties and has a significant impact on the storage stability. In order to keep the quality of the coating within the desired narrow limits it is necessary to control the manufacturing process of the coating accurately.

20 In an industrial plant for coating pharmaceutical products, selected process parameters are monitored and controlled to achieve a desired quality of the end product. Such process parameters are generally global and could include, for example, the pressure in the coating vessel, the flow rate and temperature of gas and coating liquid supplied to the coating vessel, etc. However, the influence of such global process parameters on the 25 coating process, and ultimately on the coating properties of the end product, is known only from experience in a specific plant. Thus, a processing scheme is developed for each specific plant by extensive testing. When, for example, the size or shape of the coating vessel is changed during scaling up of the process, the local environment of the particles may be altered. This calls for time-consuming measurements and adjustments in order to 30 regain the same coating properties of the end product.

There is also a need to improve existing manufacturing processes as well as to improve existing plants. Today, this is a laborious task since the influence of any change in 35 the process scheme or the plant design on the end product has to be investigated by

extensive testing, often in full scale. The same applies to the development of new products, for example when a new type of particle or coating liquid should be used.

An attempt to fulfil the above-identified needs is disclosed in the article "Fluidized bed spray granulation, investigation of the coating process on a single sphere" by K. C. Link and E.-U. Schlünder, published in Chemical Engineering and Processing, No. 36, 1997. A laboratory-scale apparatus is designed for analysis of a single particle, in order to investigate the fundamental physical mechanisms that lead to particle growth by layering. In this apparatus, a single aluminum sphere is made to levitate on a fluidizing air flow which is supplied by a capillary tube. Thereby, the sphere is freely and rotatably suspended at a stable location in a coating vessel. An ultrasonic nozzle arranged above this stable location is intermittently activated to generate a spray dust of coating liquid that falls down onto the sphere and forms a coating thereon. This type of nozzle generates a spray of droplets, the velocity of which is adjusted by means of a separate air flow through the nozzle. The apparatus is used for investigating the influence of different parameters, such as droplet velocity, temperature of fluidizing air, drying time, and type of coating liquid, on the thickness and morphology of the resulting coating. A rough measurement value of the overall thickness of the coating is obtained by weighing the sphere before and after the actual coating process and determining the difference in weight. The morphology of the coating is qualitatively examined by arranging the sphere, once coated, in a scanning-electron-microscope (SEM). For both of these measurements, the sphere must be removed from the apparatus for analysis. The apparatus also includes a lamp for illumination of the sphere and a video camera for continuous and qualitative observation of the contours of the sphere during the coating process.

25

One drawback of this prior-art apparatus resides in the difficulty to make quantitative, time-resolved measurements of coating properties. After a specific time period, the coating process must be interrupted for analysis of the coating on the sphere, whereupon a new and non-coated sphere must be subjected to a new coating process for a longer time period, and so on. In this approach, the formation of a coherent time series of measurement data requires that identical conditions are maintained in the environment of each sphere. Thus, the coating process must be repeated in exactly the same manner for each sphere. This is difficult. For example, any small variations in the masses of the aluminum spheres will necessitate an adjustment in the flow rate of the fluidizing air, to maintain each sphere at the same location in the vessel. Such a change in flow rate will also change the environment of the sphere during the coating process, thereby making it

35

difficult to compile the measurement data from several consecutive measurements into a coherent time series.

A further drawback of this known apparatus is that only a few properties of the coating, i.e. average thickness and surface morphology, can be measured.

Another drawback is that the course of a coating process can only be studied on standardized spheres, so that the coating process can be repeated in exactly the same manner for each sphere. However, the coating process is believed to be highly dependent on the properties of the particle itself, such as the size, density, porosity and shape of the particle. Thus, it may be difficult, or even impossible, to draw any conclusions for a realistic particle from experiments made in the known apparatus.

Summary of the invention

The object of the invention is to solve or alleviate some or all of the problems described above. More specifically, the method and apparatus according to the invention should allow for time-resolved measurements of coating properties on any type of particle.

This object is achieved by the method and apparatus set forth in the appended claims.

The inventive method and apparatus will allow for continuous and non-invasive monitoring of one or more principal parameters related to the coating, such as thickness, thickness growth rate and physical and/or chemical properties related to the quality of the coating, as well as heat, mass and momentum transfer, during the coating process on a single particle. The results of the measurements made possible by the inventive apparatus and method can be used to develop a fundamental model of the coating process on a single particle as a function of one or more control parameters, which can be related to properties of the environment of the particle and to properties of the particle itself. Ultimately, such a fundamental model can be converted to an aggregate model for prediction of the influence of global process parameters on the monitored principal parameter or parameters for a large number of particles, for example in a full-scale coating process in an industrial plant. Such an aggregate model is a valuable tool that can be used to scale up processes and plants, improve existing manufacturing processes and plants, and develop new products.

It should also be noted that the invention allows for monitoring of the coating process on any type of single solid sample. Thus, in contrast to prior art technique, it is conceivable to use a realistic nucleus, such as a pellet, a tablet, or a capsule.

5 The inventive method and apparatus have the additional advantage of providing information that can be directly used in the control of a full-scale process. More specifically, by effecting a coating process on a single particle at well-controlled conditions, so that desired properties of the coating on the particle is obtained, and by continuously performing the spectrometric measurement, a desired sequence of
10 measurement values can be obtained. By effecting the same spectrometric measurement in a full-scale process, the global process parameters of this process can be controlled to yield the desired sequence of measurement values. Thereby, the full-scale process will be controlled to yield the desired properties of the coating on the particles. In practice, the sequence of measurement values could form a desired trajectory in a space that is defined
15 by one or more principal components. These principal components can be derived by applying chemometric methods to measurement data obtained from a time-series of spectrometric measurements. Evidently, the desired sequence of measurement values could also be established by effecting a spectrometric measurement on a batch of particles in the full-scale process itself. However, by means of the invention, the desired sequence of
20 measurement values is established much faster, since the coating process of a single particle is considerably shorter in time than the coating process of a batch of particles in a full-scale process.

In an alternative approach for direct control of a full-scale process, the inventive
25 method and apparatus are used to identify the interrelationship between control parameters, given by conventional sensors, and principal parameters, given by spectrometric methods. This is typically done by effecting a coating process on a single particle at well-controlled conditions, and by continuously performing a spectrometric measurement and simultaneously performing a measurement of one or more control parameters, such as a
30 fluidizing gas flow rate or a temperature. By identifying relevant control parameters in this way, the inventive method and apparatus could be used to establish a desired sequence of control parameter values. This sequence could then be directly transferred to a full-scale process, wherein the global process parameters of this process are controlled to form a corresponding desired sequence of global process parameter values. Thereby, the full-scale
35 process will be controlled to yield the desired properties of the coating on the particles.

Preferably, the step of forming the coating on the particle includes generating a single droplet of a coating fluid and making the droplet impinge on the particle. The use of a single droplet, or a sequence of such single droplets, instead of a spray dust, provides for a controlled deposition of coating fluid on the particle surface. Thus, the droplet size or the droplet generating rate can be controlled during a wetting period and be used as well-defined control parameters. The term "coating fluid" is used as a comprehensive expression encompassing everything from a pure coating liquid to a slurry or suspension of coating liquid and coating solids. Alternatively, the coating fluid could be a mixture of coating solids and a carrier gas. In this case, the term "coating droplet" would refer to a coating solid.

Preferably, the particle is fluidized on an upwardly directed gas flow, so that the particle is held at a given spatial location, while being freely rotatable at this location. Thus, the particle can be fixed so that a precise measurement can be effected, and rotating so that a uniform coating can be formed. The fluidizing gas flow has the additional function of drying the particle.

It is preferred that each droplet upon generation is moved into and allowed to follow the fluidizing gas flow to the particle. Thereby it is assured that each droplet impinges on the fluidized particle.

In another preferred embodiment, the control parameter is changed based, at least partly, on the measurement value. This type of feed-back control provides for in-line adjustments of the coating process on the single particle. Thereby it is possible to monitor the effects of a change in any control parameter during the coating process.

The control parameter could include a property of said gas flow, such as a flow rate, a temperature or a content of a solvent, for example water; a property of the particle, such as a size, a shape, a density or a porosity; a property of the droplets, such as a droplet size, a droplet generation rate or a concentration of a droplet constituent; a duration of a wetting period during the coating process; and a duration of a drying period during the coating process. In addition to the control parameters listed above, there are also other parameters not listed here.

Preferably, the spectrometric measurement is performed by means of near infrared spectrometry and/or a spectrometric method based on Raman scattering and/or a

spectrometric method based on absorption in the UV, visible, or infra-red (IR) wavelength region, or luminescence, such as fluorescence emission, and/or imaging spectrometry.

Brief description of the drawings

5 In the following, a presently preferred embodiment of the invention, will be described in more detail, reference being made to the accompanying drawing which schematically shows a layout of a monitoring apparatus.

Description of a preferred embodiment

10 The monitoring apparatus disclosed on the drawing comprises a coating chamber 1, a gas supply unit 2, a coating liquid dispenser 3, a spectrometric measurement unit 4, and a main control unit 5. In the coating chamber 1, the coating process of a single particle P can be continuously and non-invasively monitored under well-controlled conditions.

15 A vertical tube 6 extends from a bottom portion 7 of the chamber 1 along a vertical center line of the chamber 1. The gas supply unit 2 is adapted to feed a gas in controlled amounts to the chamber 1. The unit 2 communicates with the tube 6 and a periphery portion 8 of the chamber 1. The flow of gas through the tube 6 is used to levitate or fluidize the particle at a given position in the chamber 1. The flow of shielding gas to the periphery
20 portion 8 is used to minimize any gradients between the measurement unit 4 and the particle P, since such gradients might introduce errors in the spectrometric measurements. Although not shown on the drawing, it is realized that such shielding gas could be supplied to the periphery portion 8 at several locations around the perimeter of the chamber 1. Alternatively, or additionally, shielding gas could be fed through the bottom portion 7.

25 A control system is provided to accurately position the particle P. The control system includes a position sensor 9, for example an array detector, which is arranged at the periphery of the chamber 1 and is adapted to output a position signal indicating to the position of the particle P. The position signal is fed to the main control unit 5, which
30 adjusts the gas flow rate accordingly by feeding a control signal to the gas supply unit 2. The control system is capable of maintaining the particle P at a given position in the chamber 1. This position might be changed over time in a controlled manner, or be spatially fixed in the chamber 1.

35 The gas supply unit 2 is also adapted to condition the gas, for example by changing the gas temperature or the gas content of a solvent, such as water, based on corresponding

control signals received from the main control unit 5. To this end, the gas supply unit 2 could include a conventional bubbler system (not shown), in which the gas is bubbled through a liquid source to add a small concentration of liquid vapor to the gas. Such, and other, high-precision systems for mixing gas and liquid vapor are available on the market.

One or more coating liquid dispensers 3 (only one shown on the drawing) is connected to the tube 6 and is adapted to sequentially generate droplets D of a coating liquid. The generated droplets D are injected into the gas flow in the tube 6 and will, by following the gas flow to the particle P, impinge on the particle P and form a coating thereon. The coating liquid dispenser 3 receives control signals, indicating for example the desired droplet generation rate and droplet size, from the main control unit 5.

In the illustrated example, the coating liquid dispenser 3 is a flow-through microdispenser of the type disclosed in the article "Design and development of a silicon microfabricated flow-through dispenser for on-line picolitre sample handling", Journal of Micromechanical Microengineering No. 9, pp 369-376, 1999, by T. Laurell, L. Wallman and J. Nilsson. This microdispenser, of which no details are given in the drawing, comprises two joined silicon structures forming a flow-through channel. A piezoceramic element is connected to one of the silicon structures. By activating the piezoceramic element, a pressure pulse is generated in the channel, thereby ejecting a droplet from an orifice in the opposite silicon structure. This microdispenser allows for sequential generation of droplets with a well-defined size and frequency.

The spectrometric measurement unit 4 is arranged at the periphery of the chamber 1 and is adapted to perform a spectrometric measurement, preferably by NIRS (Near Infrared Spectrometry), on the coating during the coating process. The resulting measurement data are represented in a sample vector. The spectrometric measurement unit 4 is also adapted to evaluate the measurement data in the sample vector and derive a measurement value related to the coating. This measurement value is fed to the main control unit 5 for storage.

NIRS provides both physical and chemical properties of the coating. This spectrometric method, like several other commonly used spectrometric methods, is non-invasive as well as non-destructive. A NIRS measurement is fast and therefore, it is employable for continuously measuring samples of all kinds. The possibilities obtained by NIRS measurements will be further discussed below.

Further, with a spectrometric measurement according to the invention, it is possible to extract information from several different depths of the coating, i.e. from the surface as well from deeper levels thereof. Additionally, it is possible to directly measure the thickness of the coating. The spectrometric measurement can be carried out in such a manner that the particle P, the coating thickness of which is to be measured, is positioned at a desired level with respect to the measurement unit 4. Thus, the mean coating thickness or a variation of the coating thickness can be measured. By employing imaging spectrometry, local inhomogeneities in the coating can be measured. Imaging spectrometry also allows for variations in the position of the particle P during the spectrometric measurement.

In the spectrometric measurement unit 4, the sample vector is evaluated in order to extract information directly related to the quality of the coating. In one embodiment, the evaluation is performed by subjecting the sample vector to a mathematical analysis, weighting the data, in conjunction to previous data, and condensing them to at least one measurement value. In the present embodiment chemometric methods are used. More particularly and at least in the case of continuous measurements during the coating process, a multivariate analysis, such as PCA (Principal Component Analysis), or PLS (Partial Least Squares) is performed on the sample vector.

In this way, it is possible to directly measure the quality of the coating, in terms of relevant physical and/or chemical properties. As a further example, the heat transfer to the coating can be monitored by way of extracting a measurement value related to the surface temperature of the coating. Further, the mass transfer to the coating can be monitored by way of extracting a measurement value related to the moisture content of the coating.

The main control unit 5, for example a personal computer, is adapted to continuously store control parameters potentially affecting the coating process on the particle P in the chamber 1. Some control parameters are mentioned above, for example the gas temperature, the gas humidity, the droplet generation rate, and the droplet size. The main control unit receives additional control parameter information from a temperature sensor 10a, a mass flow meter 11 and a gas analyzer 12 arranged to measure the temperature, the flow rate and the solvent concentration, respectively, of the gas entering chamber 1 through tube 6, as well as a temperature sensor 13 and a gas analyzer 14 arranged to measure the temperature and the solvent concentration, respectively, of the gas leaving chamber 1. Additionally, a temperature sensor 10b is arranged to measure the

temperature of the shielding gas entering the chamber 1. Other such conventional sensors could be provided. Further control parameters could include the duty cycle of the coating liquid dispenser 3, i.e. the time period with wetting and drying, respectively, of the particle P. Further control parameters could be related to the particle P itself, or the concentration of a constituent of the coating liquid.

It is appreciated that one or more control parameters could be changed during the coating process, for monitoring its influence on the properties of the coating, as measured by the unit 4.

Examples of possible modifications comprise for example the use of other spectrometric methods, such as those based on Raman scattering, or absorption in the UV and visible or infrared (IR) wavelength regions or luminescence such as fluorescence emission.

Another example of a modification substitutes a more simple analysis to the chemometric methods as follows. Generally, when using spectrometric methods, broad response spectra are obtained. However, instead of analysing all of the measurement values obtained over such a broad response spectrum by applying chemometric methods, merely one or a few values of the measurement values are analysed. For example, the measurement values at a few individual frequencies could be analysed. Also, when employing Raman spectrometry, which often results in values well separated by wavelength, this simplified analysis can be useful.

CLAIMS

1. A method of monitoring the formation of a coating on a single particle (P), comprising the steps of: arranging the particle (P) at a given spatial location; forming said coating on the particle (P); and obtaining a measurement value of at least one principal parameter related to said coating, c h a r a c t e r i z e d in that said measurement value is obtained by performing a spectrometric measurement on said coating during said step of forming said coating.

2. A method as set forth in claim 1, wherein said spectrometric measurement is performed continuously during at least part of the step of forming said coating, thereby generating a sequence of measurement values of said at least one principal parameter.

3. A method as set forth in claim 1 or 2, wherein said step of arranging the particle (P) at a given spatial location includes fluidizing said particle (P) on an upwardly directed gas flow.

4. A method as set forth in any one of claims 1-3, wherein said step of forming said coating on the particle (P) includes generating a single droplet (D) of a fluid, and bringing said droplet to impinge on said particle (P).

5. A method as set forth in claims 3 and 4, wherein said droplet (D) upon said generation is moved into and allowed to follow said upwardly directed gas flow to said particle (P).

6. A method as set forth in claim 4 or 5, wherein said single droplet (D) is repeatedly generated, thereby forming at least one stream of such droplets (D) that sequentially impinge on said particle (P).

7. A method as set forth in any one of the preceding claims, further comprising a step of monitoring at least one control parameter related to the environment of the particle (P) or the particle (P) itself, and a step of identifying a functional relationship between said at least one control parameter and said at least one principal parameter.

8. A method as set forth in claim 7, further comprising a step of generating, based on said functional relationship for said single particle (P), an aggregate model for

prediction of the influence of said at least one control parameter on said at least one principal parameter for a large number of such particles (P).

9. A method as set forth in claim 7 or 8, further comprising the step of changing
5 said at least one control parameter based, at least partly, on said measurement value.

10. A method as set forth in any one of claims 7-9 in combination with claim 3 or 5,
wherein said at least one control parameter includes a property of said gas flow, such as a
flow rate, a temperature or a content of a solvent.

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11. A method as set forth in any one of claims 7-9, wherein said at least one control
parameter includes a property of the particle (P), such as a size, a shape, a density or a
porosity.

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12. A method as set forth in any one of claims 7-9 in combination with any one of
claims 4-6, wherein said at least one control parameter includes a property of said droplet
(D), such as a droplet size, a droplet generation rate or a concentration of a droplet
constituent.

20

13. A method as set forth in any one of claims 7-9 in combination with any one of
claims 4-6, wherein said at least one control parameter includes a duration of a wetting
period during said step of forming said coating, said wetting period being effected by
controlling said droplet generation.

25

14. A method as set forth in any one of claims 7-9 in combination with any one of
claims 4-6, wherein said at least one control parameter includes a duration of a drying
period during said step of forming said coating.

15. A method as set forth in any one of the preceding claims, wherein said step of
30 obtaining said measurement value includes generating a sample vector of measurement
data from said spectrometric measurement, and condensing said measurement data into
said measurement value of said at least one principal parameter.

16. A method as set forth in any one of the preceding claims, wherein said
35 spectrometric measurement is performed by means of near-infrared spectrometry

17. A method as set forth in any one of the preceding claims, wherein said spectrometric measurement is performed by means of a spectrometric method based on Raman scattering.

5 18. A method as set forth in any one of the preceding claims, wherein said spectrometric measurement is performed by means of a spectrometric method based on absorption in the UV, visible, or infrared (IR) wavelength region, or luminescence, such as fluorescence emission.

10 19. A method as set forth in any one of the preceding claims, wherein said spectrometric measurement is performed by means of imaging spectrometry.

20. A method as set forth in any one of the preceding claims, wherein said particle (P) is a pharmaceutical product, such as a pellet a tablet or a capsule.

15 21. Use of a method as set forth in any one of the preceding claims for identifying a functional relationship between said at least one principal parameter and properties of an environment of the particle (P) during the formation of said coating, and/or properties of the particle (P) itself.

20 22. Use of a method as set forth in claim 2 for control of a coating process of a batch of particles, wherein said sequence of measurement values is used as a sequence of reference values in said control, and wherein a corresponding spectroscopic measurement is effected on said batch of particles to provide a sequence of actual values for said control.

25 23. Use of a method as set forth in any one of claims 1-20 for control of a coating process of a batch of particles, wherein a functional relationship is identified between said at least one principal parameter and at least one simultaneously monitored control parameter, which is related to an environment of said single particle (P); wherein one or
30 more of said at least one control parameters, based on said functional relationship, is selected to represent one or more of said at least one principal parameters; wherein a desired sequence of values of said one or more selected control parameters is determined for said single particle (P); and wherein said coating process of a batch of particles is controlled based on said desired sequence of selected control parameter values.

24. An apparatus for monitoring the formation of a coating on a single particle (P), comprising means (2, 5, 6, 9) for arranging said particle (P) at a given spatial location, and a fluid supply unit (3) adapted to apply a coating fluid to said particle (P) such that said coating is formed, c h a r a c t e r i z e d by a measurement unit (4) which is adapted
5 to perform a spectrometric measurement on said coating during formation thereof, and to derive a measurement value of at least one principal parameter related to said coating.

25. An apparatus as set forth in claim 24, wherein said measurement unit (4) is adapted to continuously perform said spectrometric measurement, thereby generating a
10 sequence of measurement values of said at least one principal parameter.

26. An apparatus as set forth in claim 24 or 25, wherein said particle arranging means (2, 5, 6, 9) comprises a flow unit (2) which is adapted to generate a fluidizing gas flow on which the particle (P) is fluidized.
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27. An apparatus as set forth in claim 26, further comprising a housing (1) in which said coating is formed on said particle (P), wherein said flow unit (2) is adapted to provide a shielding gas inside the housing (1) intermediate the measurement unit (4) and the location of said particle (P), said shielding gas being essentially identical to the gas used
20 for fluidizing said particle (P).

28. An apparatus as set forth in any one of claims 24-27, wherein said fluid supply unit (3) is operable to generate a single droplet (D) that is brought to impinge on said particle (P).
25

29. An apparatus as set forth in claim 26 and 28, wherein said fluid supply unit (3) is arranged to inject each droplet (D) into said fluidizing gas flow.

30. An apparatus as set forth in claim 28 or 29, wherein said fluid supply unit (3) is
30 arranged to repeatedly generate said single droplet (D), thereby forming a stream of such droplets (D) that sequentially impinge on said particle (P).

31. An apparatus as set forth in any one of claims 24-30, further comprising a control unit (5) which is adapted to monitor at least one control parameter related to the
35 environment of the particle (P) or the particle (P) itself

32. An apparatus as set forth in claim 31, wherein the control unit (5) is adapted to receive said measurement value from said measurement unit (4) and to effect a change of said at least one control parameter based, at least partly, on said measurement value.

33. An apparatus as set forth in claim 32 in combination with claim 26 or 28, wherein said at least one control parameter includes a property of said fluidizing gas flow, such as a flow rate, a moisture content or a temperature, and wherein said control unit (5) is operable to effect said change by controlling said flow unit (2).

34. An apparatus as set forth in claim 32 in combination with any one of claims 28-30, wherein said at least one control parameter includes a property of said droplets, such as a droplet size, a droplet generation rate or a concentration of a droplet constituent, and wherein said control unit (5) is operable to effect said change by controlling said fluid supply unit (3).

35. An apparatus as set forth in claim 32 in combination with any one of claims 28-30, wherein said at least one control parameter includes a duration of a droplet generation period, and wherein said control unit (5) is operable to effect said change by controlling said fluid supply unit (3).

36. An apparatus as set forth in claim 32 in combination with any one of claims 28-30, wherein said at least one control parameter includes a duration of a drying period, and wherein said control unit is operable to effect said change by controlling said fluid supply unit (3).

37. An apparatus as set forth in any one of claims 24-36, wherein said measurement unit (4) is adapted to perform said spectrometric measurement by means of near-infrared spectrometry.

38. An apparatus as set forth in any one of claims 24-37, wherein said measurement unit (4) is adapted to perform said spectrometric measurement by means of a spectrometric method based on Raman scattering.

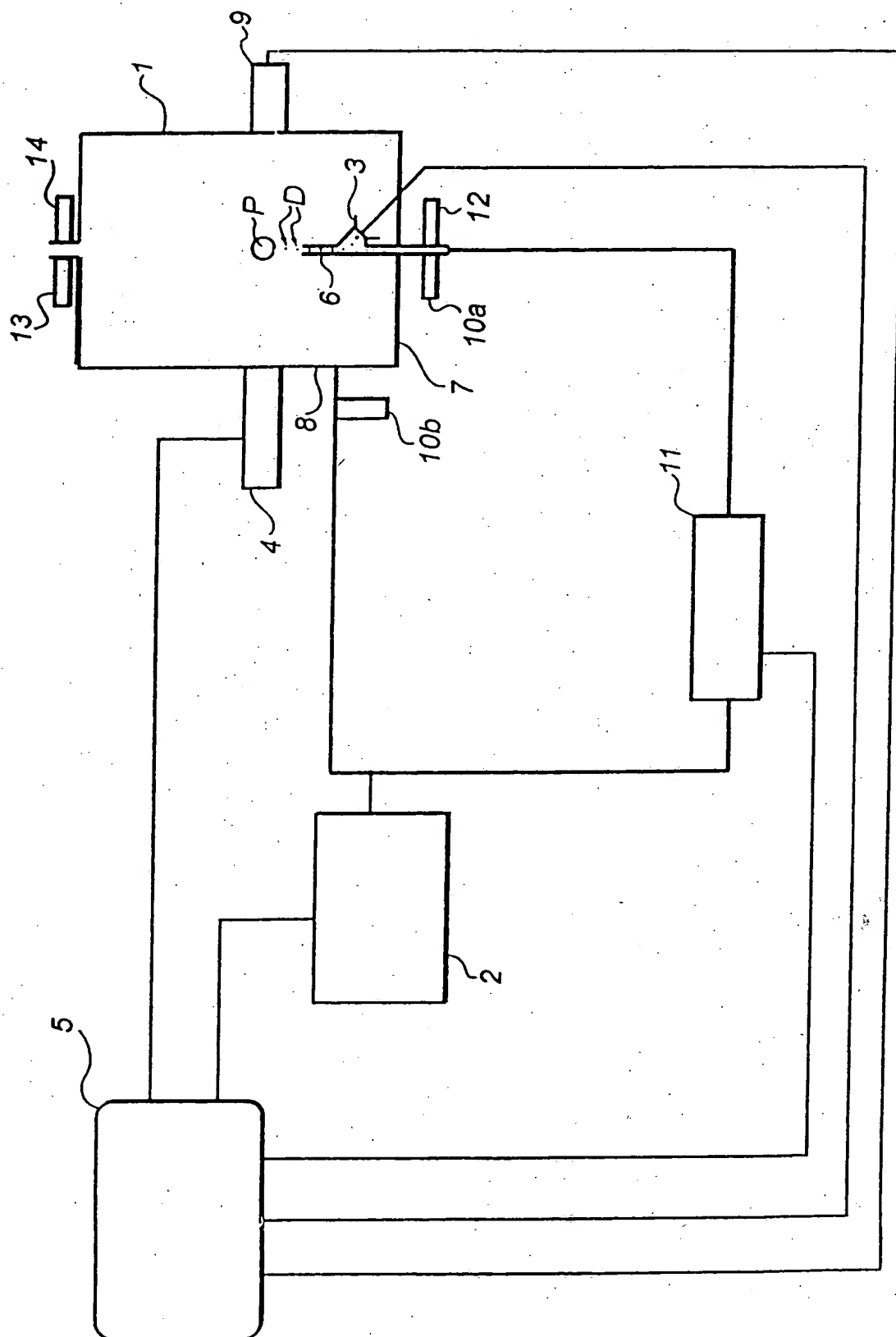
39. An apparatus as set forth in any one of claims 24-38, said measurement unit (4) is adapted to perform said spectrometric measurement by means of a spectrometric method

based on absorption in the UV, visible, or infrared (IR) wavelength region, or luminescence, such as fluorescence emission.

40. An apparatus as set forth in any one of claims 24-39, wherein said measurement unit (4) is adapted to perform said spectrometric measurement by means of imaging spectrometry.

41. An apparatus as set forth in any one of claims 24-40, wherein said particle (P) is a pharmaceutical product, such as a pellet, a tablet or a capsule.

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INTERNATIONAL SEARCH REPORT
Information on patent family members

02/04/01

International application No.
PCT/SE 01/00023

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
US	5518759	A	21/05/96	US 5405645 A	11/04/95
WO	003229	A1	20/01/00	NONE	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00023

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 21/05, G01N 21/85, B05D 1/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01B, G01J, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5518759 A (SEVILLANO ET AL), 21 May 1996 (21.05.96), figures 1,7	1,2,24,25
Y	figures 1,7	3,4,26
Y	WATANO,S.et al."CONTROL OF GRANULATION PROCESS BY FUZZY LOGIC". IN:NORTH AMERICAN FUZZY INFORMATION, 1999.18TH.INTERNATIONAL CONFERENCE OF THE,NAFIPS On pages:905-908, 10-12 June 1999.fig.2	3,26
Y	T.Laurell et al."DESIGN AND DEVELOPMENT OF A SILICON MICROFABRICATED FLOW-THROUGH DISPENSER FOR ON-LINE PICOLITRE SAMPLE HANDLING". J.MICROMECH.MICROENG.9(1999)369-376.Printed in the UK.Abstract.	4

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00023

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 003229 A1 (ASTRA AKTIEBOLAG), 20 January 2000 (20.01.00), abstract -----	1,2,7-20, 21-25,31-41